REMARKS

In paragraph 4, on page 2 of the Office Action, the Examiner rejects Claims 9-10 under 35 U.S.C. § 112, first paragraph as containing new matter.

Specifically, the Examiner states that step (c) of Claim 9 constitutes new matter. The Examiner notes that Applicants indicate that support can be found at page 30 of the specification. However, the Examiner contends that page 30 only discloses original Claims 1-5.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

As indicated at page 29, line 3 from the bottom of the specification, mice were given total body irridiation in a dose of 7.0 Gy, 6.5 Gy or 6.0 Gy. Thereafter, bone marrow cells were administered by portal injection. Then, skin grafting was performed within the same day, i.e., transplanting an organ into the recipient. As taught at page 30 of the specification, the engraftment rate was 100% when using a radiation dose of 7.0 Gy, whereas in the recipient mice exposed to a radiation dose of 6.0 Gy, the skin graft was rejected in all of the mice. Further, successful engraftment was obtained in 3 of 3 recipient mice in the portal administration group given a radiation dose of 6.5 Gy. Thus, Applicants respectfully submit that pages 29-30 clearly support step (c) of Claim 9.

Accordingly, Applicants respectfully submit that step (c) does not constitute mew matter, and thus request withdrawal of the Examiner's rejection.

In paragraph 6, on page 3 of the Office Action, the Examiner rejects Claims 9-10 under 35 U.S.C. § 103 as being

unpatentable over Slavin et al in view of Ildstad and Zhang et al.

Specifically, the Examiner states that Slavin et al teaches a method of inducing immunological tolerance in an organ transplantation recipient by subjecting the recipient to sublethal total body irradiation and administering to the recipient whole bone marrow, where transplanting of the organ in the recipient occurs within the same day as whole bone marrow cells are administered, and wherein an engraftment rate of 100% is achieved. The Examiner notes that Slavin et al does not teach a sublethal total body irradiation of at least 6.5 Gy or 6.5 to 7.0 Gy and administering the whole bone marrow cells by hepatic portal administration.

However, the Examiner states that Ildstad et al teaches organ grafting by subjecting the recipient to sublethal total body irradiation and administering to the recipient whole bone marrow to achieve a 100% engraftment in recipients at 7.0 Gy; and Zhang et al teaches both intravenous and portal injection of bone marrow cells. Hence, the Examiner concludes that it would have been obvious to apply the sublethal dose taught in Ildstad et al and the portal administration taught in Zhang et al in the method of Slavin et al to achieve the present invention.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Applicants respectfully submit that the Examiner's rejection is improper because total body irradiation (TBI) is not conducted in Slavin et al. An essential technical feature of Slavin et al is "administering a short course of total lymphoid irradiation (TLI)." This is clear from the

descriptions in Slavin et al (see page 13, lines 50-67; Example 14 and Claim 1).

TBI, employed in the present invention, is fundamentally different from TLI as employed in Slavin et al.

TLI is a technique wherein lymph nodes are irradiated with radiation. This technique is effective at eliminating mature lymphocytes, but the radiation does not reach bone marrow cells. Therefore, hematopoietic stem cells (HSCs, i.e., immature and undifferentiated lymphocytes) that exist in the bone marrow cells never get attacked. In other words, in the TLI technique, the immune system of a recipient is temporarily damaged by severely depleting the lymphocytes, but gradually recovers from the damage with the passage of time, because HSCs of the recipient remain in the bone marrow cells. In this sense, the technique disclosed by Slavin et al uses mixed allogenic chimerism. However, it is known that the technique disclosed by Slavin et al has the disadvantage that, because the hematopoietic system of the recipient survives, the number of HSCs derived from the graft donor gradually decreases and only the hematopoietic system of the recipient remains in the end.

On the other hand, in TBI as employed in the present invention, all of the lymphocytes and HSCs in the bone marrow cells of the recipient are damaged by total body irradiation. Under such conditions, when whole bone marrow cells (WBMCs) from a graft donor are administered to the recipient, the immune system of the recipient is replaced with that of the donor (fully allogenic chimerism). Slavin et al does not teach such TBI, and the hematopoietic system formed in Slavin et al is totally different from that of the present invention.

"Mixed" allogenic chimelism is fundamentally different from "fully" allogenic chimerism, as demonstrated by Jin et al, *Transplantation*, 71(12):1725-1731 (2001), provided to the Examiner with the Amendment filed November 26, 2002.

The Examiner is requested to particularly note sections "Chimerism and Tolerance" (page 1727), "Evidence for Acceptance of Allogenic Skin, Pancreas, and Adrenal Glands" (page 1728), and "Discussion" (pages 1728-1730).

Hence, Slavin et al clearly teaches away from the present invention.

More specifically, Slavin et al teaches that TBI is undesirable (at page 8, lines 63-65):

> Due to its non-selective effects on all of the host's hematopoietic cells and its severe immediate and long-term side effects, TBI is not preferred.

From this teaching, one skilled in the art would never think of combining TBI, taught by Ildstad, with Slavin et al. Furthermore, the same effects as disclosed by Slavin et al would never be achievable by conducting such TBI.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Slavin et al and for the following reasons, it is clear that Ildstad et al and Zhang et al do not provide the deficiencies that exist therein.

As the Examiner acknowledges, an important factor that differentiates the present invention from Ildstad is that, in the present invention, WBMCs (whole blood marrow cells) are administered by PV (portal venous administration), and organ transplantation is performed within the same day of PV (one-day protocol).

The steps according to Claim 9 involve,

(a) conducting TBI (total body irradiation) using a radiation dose of at least 6.5 Gy,

(b) administering WBMC's by PV, and

(c) transplanting the organ within the same day (see Test Example 4 and Figure 2 as the WBMC's are administered (a one-day protocol),

a 100% engraftment rate for the organ transplanted can be achieved.

The one-day protocol of organ transplantation is highly advantageous since it enables organ transplantation from brain dead donors, whose brain function has totally ceased for 24 hours.

In contrast, organ transplantation from such donors can not be carried out by the method of Ildstad, wherein the organ transplantation is performed 1-7 months after the bone marrow call administration (see column 21, lines 60-67 in the section of "6.2.9. Evidence for Specific Tolerance *In Vivo* to Donor-Type Skin Grafts" in Ildstad).

As described above, Ildstad merely teaches skin graft conducted 1-7 months after the bone marrow cell administration. Therefore, the teachings of Ildstad would not lead a person skilled in the art to arrive at a technique by which an engraftment rate of 100% can be achieved when organ transplantation is performed according to a one-day protocol, as claimed in the present application.

Again, the method of the present invention enables hematolymphoid cells of the recipient to be completely replaced by donor-derived cells, i.e., "fully" alogenic chimerism can be

achieved, which is fundamentally different from the "mixed" allogenic chimerism taught in Ildstad (see Jin et al, *supra*).

In this respect, the technique employed in the present invention is totally different from that taught by Ildstad, and is extremely effective in organ transplantation.

As described above, Ildstad does not disclose a technique usable for a one-day protocol by which an engraftment rate of 100% can be achieved, and therefore even applying the PV injection taught by Zhang et al in the teachings of Ildstat, it is impossible to arrive at the present invention, i.e., it would still remain a technique of organ transplantation preformed 1-7 months after the PV injection).

Furthermore, as explained on page 5 of the Amendment filed May 1, 2001, Zhang et al merely teaches a technique without irradiation (TBI). A technique that does not perform TBI is fundamentally different from that of the present invention in which irradiation (TBI) is conducted. Thus, the Examiner's combination rejection can only be made in hindsight, which is legally improper.

Moreover, it is apparent to ones skilled in the art that the results obtained by the non-TBI system (TBI dose of 0 Gy) disclosed in Zhang et al can not be applied to a TBI system. In other words, a skilled artisan would not foresee the effects achieved by TBI plus PV from the teachings of Ildstad in view of Zhang et al. This is clear from the Examiner's assertion that Hayashi et al and Takao et al (of record) can not be used to infer the results of Ildstad. That is, it is the Examiner's position that even in systems with irridation, if the radiation doses are different, the results can not be inferred. Thus, in view of the Examiner's assertion, there is no way that a person

skilled in the art could predict that similar effects can be attained when the techniques used in a non-irradiation system are employed in a system with irridation.

In summary, the claims set forth an engraftment rate and a one-day administration protocol which are not taught or suggested in Zhang et al and Ildstadt. Thus, even if Ildstadt and Zhang et al were combined with Slavin et al, the present invention would not be achieved.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Slavin et al alone or when combined with the teachings of Ildstad and Zhang et al, and thus request withdrawal of the Examiner's rejection.

In view of the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the telephone number listed below on any questions that might arise.

Respectfully submitted,

Gordon Kit
Registration No. 30,764

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

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